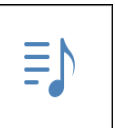
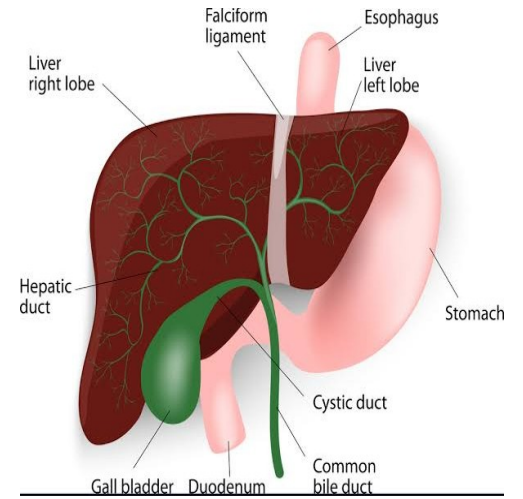




Armed Forces College of Medicine AFCM





Physiology of the Liver & Biliary secretions

By

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Ass. Prof. Physiology



INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1. Explain the major functions of the liver with respect to synthesis, metabolism, detoxification, and excretion of hydrophobic substances
2. Describe entero-hepatic circulation
3. Describe the formation of bile & its constituents
4. Explain its role in the excretion of cholesterol and bilirubin
5. Explain functions of bile salts
6. List functions of gall bladder



Functions of the liver



Liver is essential for life

It is the most important metabolic organ in the body

The liver & gall bladder are accessory organs of the alimentary tract



Functions of the liver

1- Metabolic function



1- Metabolic Function

Carbohydrate
metabolism

Fat
metabolism

Protein
metabolism



Functions of the liver

CHO metabolism



The liver plays an important role in

1- Regulation of blood glucose concentrations by either adding or removing glucose from blood according to the body needs (glucostasis)

2 - Converts galactose & fructose into glucose

I. Well fed state

II. Fasting state

Glycolysis (ATP)

Glycogenesis (glucose storage as glycogen)

Lipogenesis

Glycogenolysis

Gluconeogenesis



Functions of the liver

Fat metabolism



Fat metabolism

1- Oxidation of fatty acids → energy

2- Synthesis of

3- Lipogenesis

Cholesterol
(80% is converted to bile salts)

lipoproteins

phospholipids

(fat synthesis from CHO & proteins)

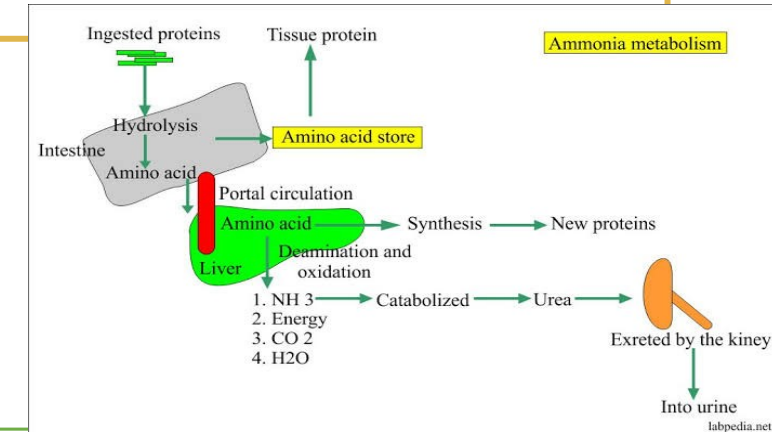


Functions of the liver

Protein metabolism



Protein metabolism



1- Deamination of amino acids → **ammonia**

2- Transformation of **ammonia** (highly toxic) → **urea** (less toxic) to be excreted in urine

3- Formation of **uric acid** which is the end product of nucleoprotein metabolism

4- Synthesis of **non - essential amino acids**

5- Synthesis of **plasma proteins**



Functions of the liver

Protein metabolism

“Synthesis of plasma proteins”



- **Albumin** is quantitatively the most significant protein synthesized by the liver, and accounts for the majority of plasma oncotic pressure
- Many of the products are **acute-phase proteins**, proteins synthesized & secreted into the plasma on exposure to stressful stimuli
- Others are **proteins that transport steroids and other hormones** in the plasma, and still others are **clotting factors**
- The only major class of plasma proteins not synthesized by the liver are the **immunoglobulins**

liver failure □
Decreased plasma protein (albumin) □
Decreased oncotic pressure □
edema



Functions of the liver

2- Formation and secretion of bile



Hepatocytes form & secrete 600-1200 ml/day Bile

(containing bile salts & bile pigments)

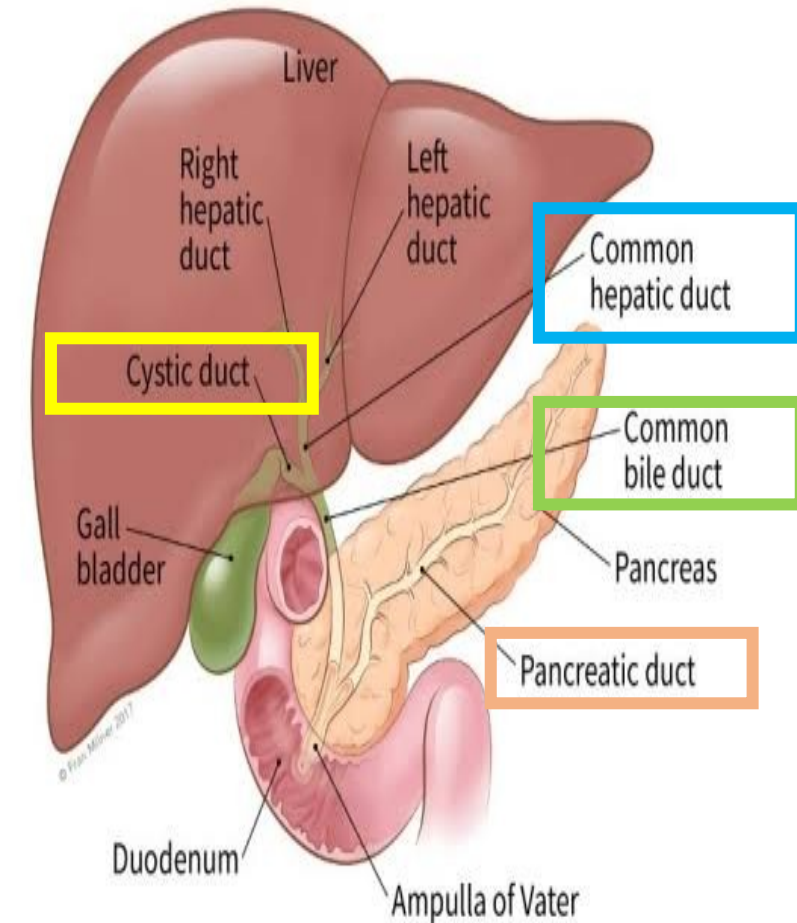
□ bile canaliculi □ Stored in gall bladder □ Emptied into the duodenal lumen with meals

Common hepatic duct + Cystic duct □ Common bile duct (CBD)

Common bile duct (CBD) joins Pancreatic duct

→ forming the ampulla of Vater “opens in duodenum”

“guarded by the sphincter of Oddi”



Functions of the liver

3- Reservoir function



Blood reservoir

Liver stores about 200- 450 ml of blood in the hepatic veins and sinusoids

This amount can replace some of the blood lost in hemorrhage



Functions of the liver

4 -Detoxification of blood



The liver has
the ability to
detoxify &
excretes
different
substances as

Drugs & many
Toxins

e.g Pencillin,
erythromycin,
sulfonamides.

Hormones

e.g
Aldosterone,
cortisol,
thyroxine,,
estrogen.

Deamination of
amino acids →
amonia

Ammonia
→ urea

Porphyryns
→ bilirubin

Purines,..
→ uric acid



Functions of the liver

4 -Detoxification of blood



The liver has the ability to detoxify & excretes different substances as

Drugs & many Toxins

Hormones

Deamination of amino acids → ammonia

In liver failure → increased levels of circulating ammonia → Hepatic encephalopathy

In liver failure → increased levels of drugs →?????

Liver disease can result in the apparent overactivity of some hormones



Functions of the liver

5 - Endocrinal function



Endocrinal function

Secretes IGF-1 in response to GH
□ promotes growth

Secretes angiotensinogen to be changed to angiotensin I by renin

Conversion of T₃ to T₄ by deiodination

Activation of vit D₃ then, second activation in kidney □ calcium absorption

Secretes Thrombopoietin □ stimulates platelet production

Secretes Erythropoietin □ stimulates RBCs production



Functions of the liver



6 - The liver is important for erythropoiesis

Liver is important for erythropoiesis

Forms 10% of **erythropoietin**

Synthesizes the **globin** part of Hb

Stores **vitamin B12**

Stores **iron**
"Blood iron buffer function"

Stores **copper**

Erythrocytes formed in liver during fetal life

In Liver Failure □ anemia is a common finding in patients



Functions of the liver



7- The liver is important for blood clotting as it

Importance of liver for blood clotting

The liver is the only site for formation of

Fibrinogen,

Prothrombin

Factor VIII

In the presence of vitamin K,
Activation of factors

II , VII,
IX & X

In Liver Failure □ Bleeding tendency is a common finding



Functions of the liver

8 - Storage function



The liver stores

Glycogen

Fat

Vitamins
(A,D &
B12) (can
prevent
deficiency
for 10
months, 3-
4 months,
12 months
respective
ly)

Iron

Copper



Functions of the liver

9 - Cleansing function (blood filtration)

10 - Production of acute phase proteins



Kupffer cells

- Are large phagocytic macrophages that line hepatic sinusoids
- They cleanse & remove 99% of bacteria in the portal blood coming from intestine. *So, in liver failure, systemic infection is common*

In Liver Failure
systemic
infection is
common

Production of acute phase proteins

- e.g C-reactive protein (important in inflammation)



- List the different functions of liver

Bile



It is an aqueous, alkaline golden yellow juice that is secreted by the liver & s

- **Volume:** 600-1200 ml/day
- **pH** : alkaline



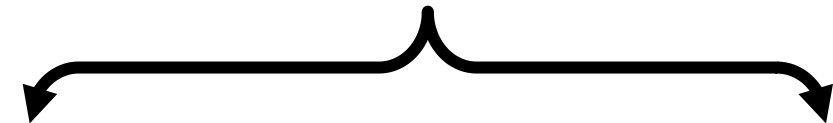
Organic constituents (2%)

Aqueous, alkaline secretion (97.5%)



- **Bile salts,**
- **Cholesterol,**
- **Lecithin &**
- **& Bilirubin**

**Secreted by
hepatocytes**



**Watery
&
Rich in NaHCO_3**

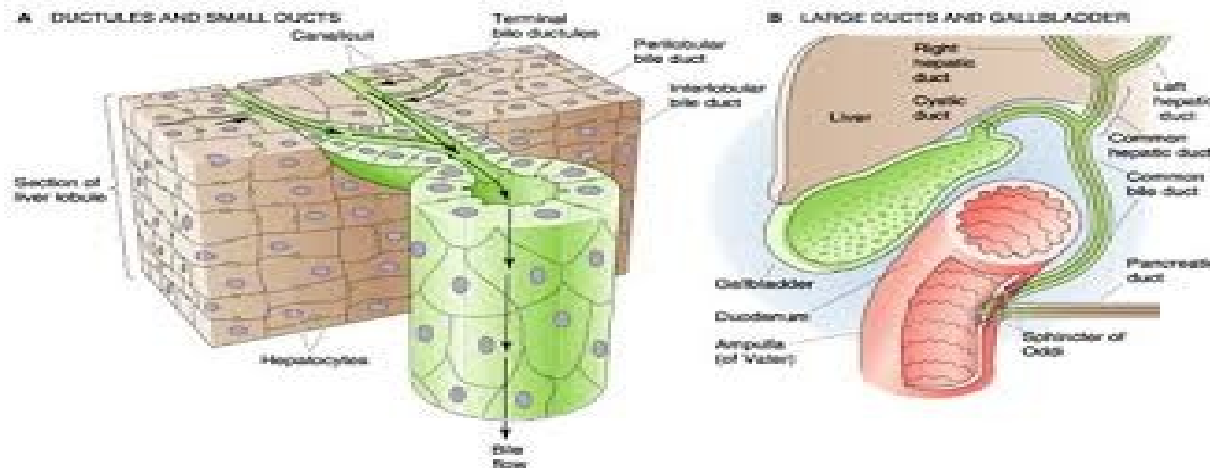
**Secreted by
duct cells**



Bile formation



Bile Formation



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Biliary Tree --Canaliculi form an extensive meshwork surrounding and draining hepatocytes

Bile from hepatocytes

Small canaliculi

Small terminal ductules (canals of Herring)

Perilobular bile ducts

Interlobular bile ducts

Septal ducts

Cystic duct (gallbladder)

Lobar ducts

Left and right hepatic ducts

Common hepatic bile duct

COMMON BILE DUCT

Pancreatic Duct (Ampulla of Vater)

Enters into duodenal lumen at
Sphincter of Oddi

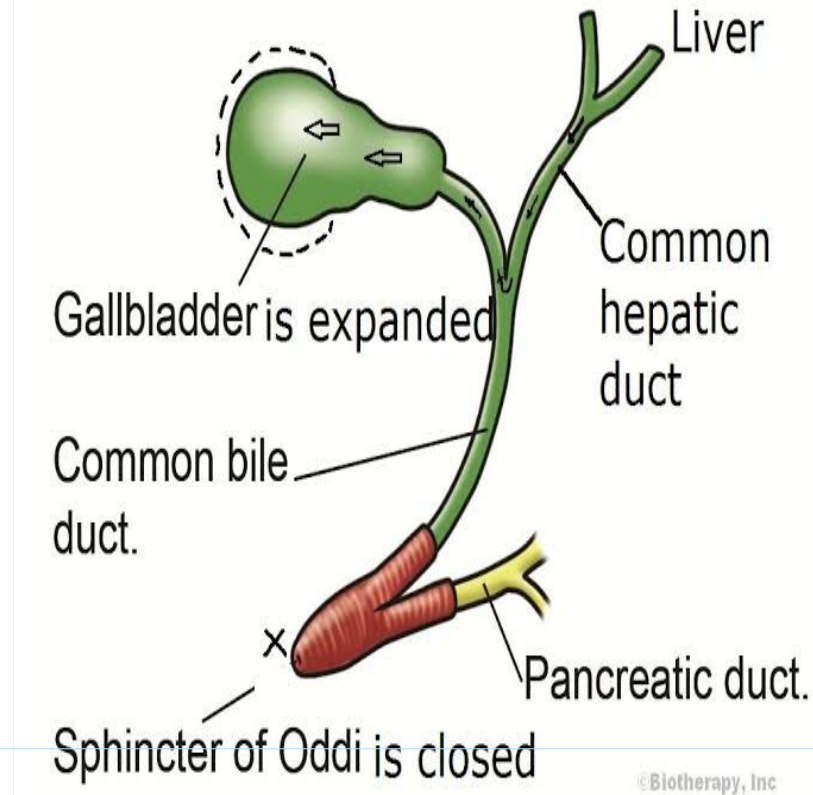


Mechanism of bile secretion



During rest (in between meals)

- Sphincter of Oddi is contracted. So, "secreted bile by the liver passes to be stored in gall bladder "GB"
- GB concentrates bile by active reabsorption of Na^+ followed by Cl^- & H_2O passively



After meals

- 95% of bile salts are reabsorbed actively from the terminal ileum, then pass into the portal circulation back to the liver

(Enterohepatic circulation of bile salts)

During meals

- Swallowing □ relax sphincter of oddi,
- When food reaches intestine ,CCK □ contraction of GB □ evacuation of bile into duodenum



Regulation of biliary secretion



Chemical **Bile salts**

The most important stimulant of bile secretion by liver cells

Hormonal Secretin CCK

Neural

Vagal stimulation during the cephalic and gastric phase of gastric secretion □

* Increases bile secretion rich in H_2O & HCO_3^-

* Contraction of gall bladder by releasing acetylcholine & Relaxation of sphincter of oddi



Regulation of biliary secretion



Hormonal

Also Gastrin
& Motilin $\uparrow$
bile
secretion

Secretin

Secreted by
intestinal mucosa
in response to
acid chyme

It stimulates
bile secretion
rich in H_2O
& HCO_3

It is a
choleretic

CCK

Secreted by
intestinal mucosa
in response to
Fatty acids &
Amino acids

It causes
strong
contraction of
GB

It is
cholagogue



Regulation of biliary secretion



Choleretic

Increase bile production (increase water and bicarbonate content of the bile)

Choleretic

1- Bile salts
(most potent)

2-Secretin hormone
Released from S cells of upper intestinal mucosa

3- Vagus nerve

Regulation of biliary secretion



Cholagogue

"Stimulate gall bladder wall contraction and relaxation of sphincter of oddi"

Cholagogue

1-Cholecystikinin hormone
Released from cells of upper intestinal mucosa

2-vagus nerve

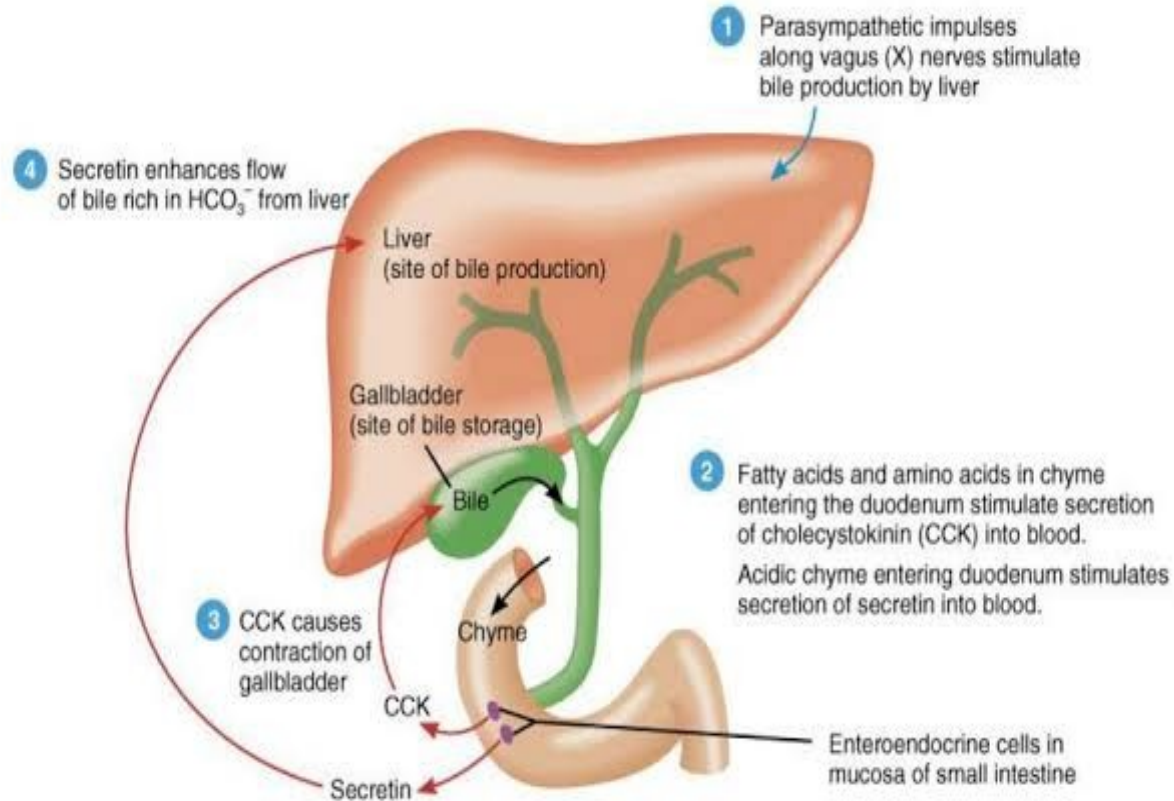
3- magnesium sulfate



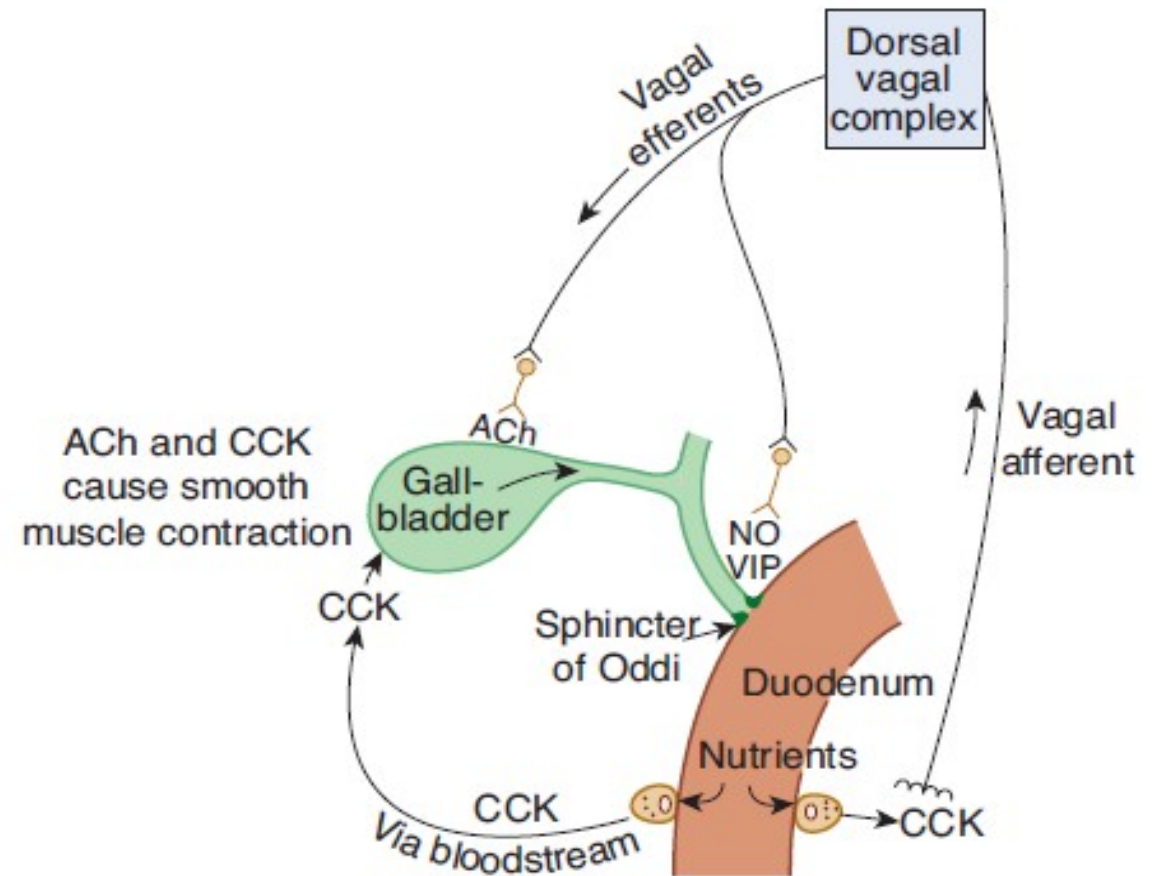
Regulation of bile secretion and gall bladder emptying



Regulation of Bile Secretion



Neurohumoral control of gallbladder contraction and biliary secretion

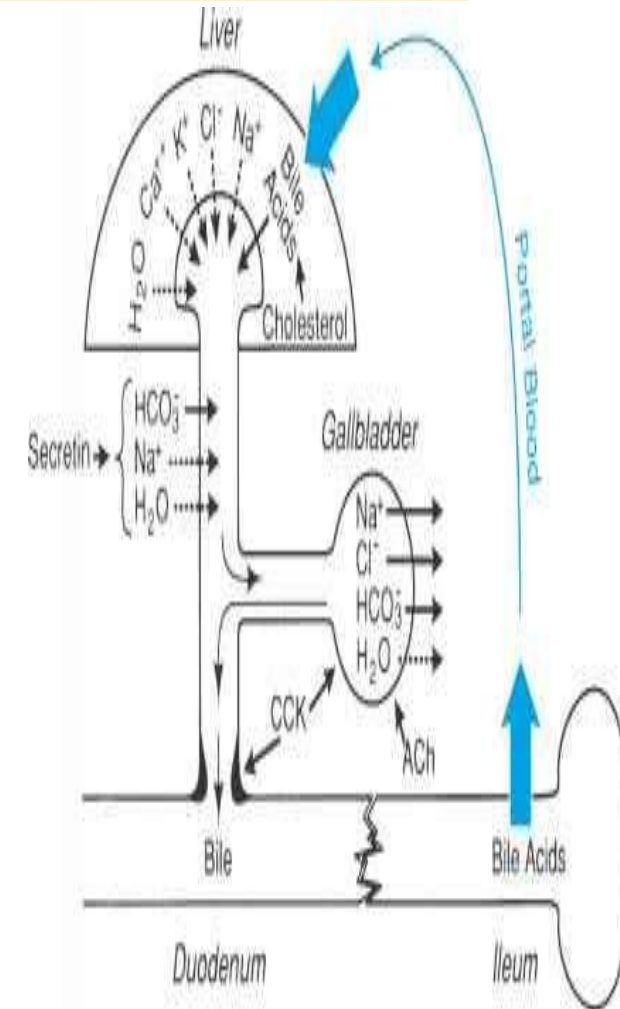
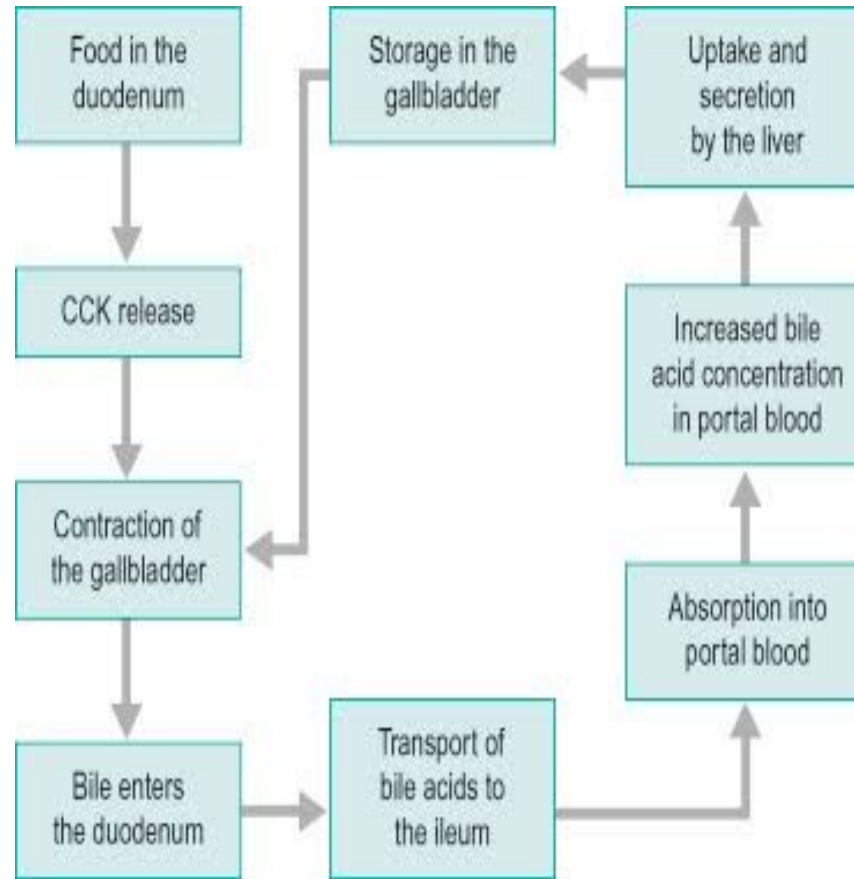
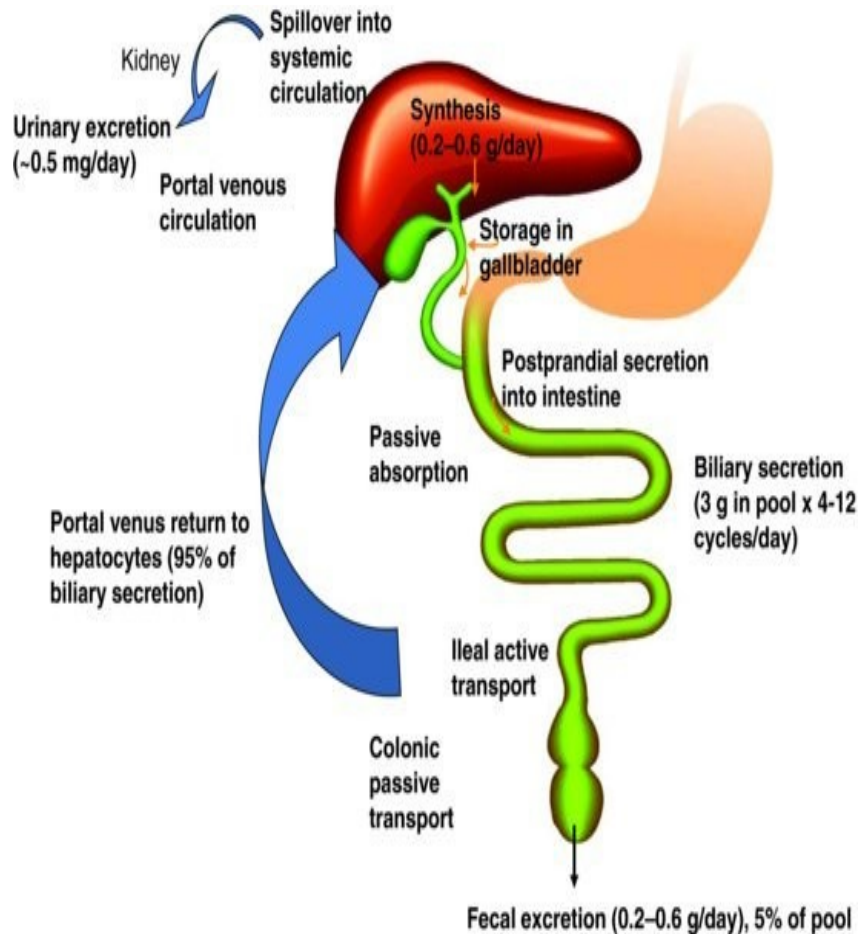


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Enterohepatic circulation of bile salts

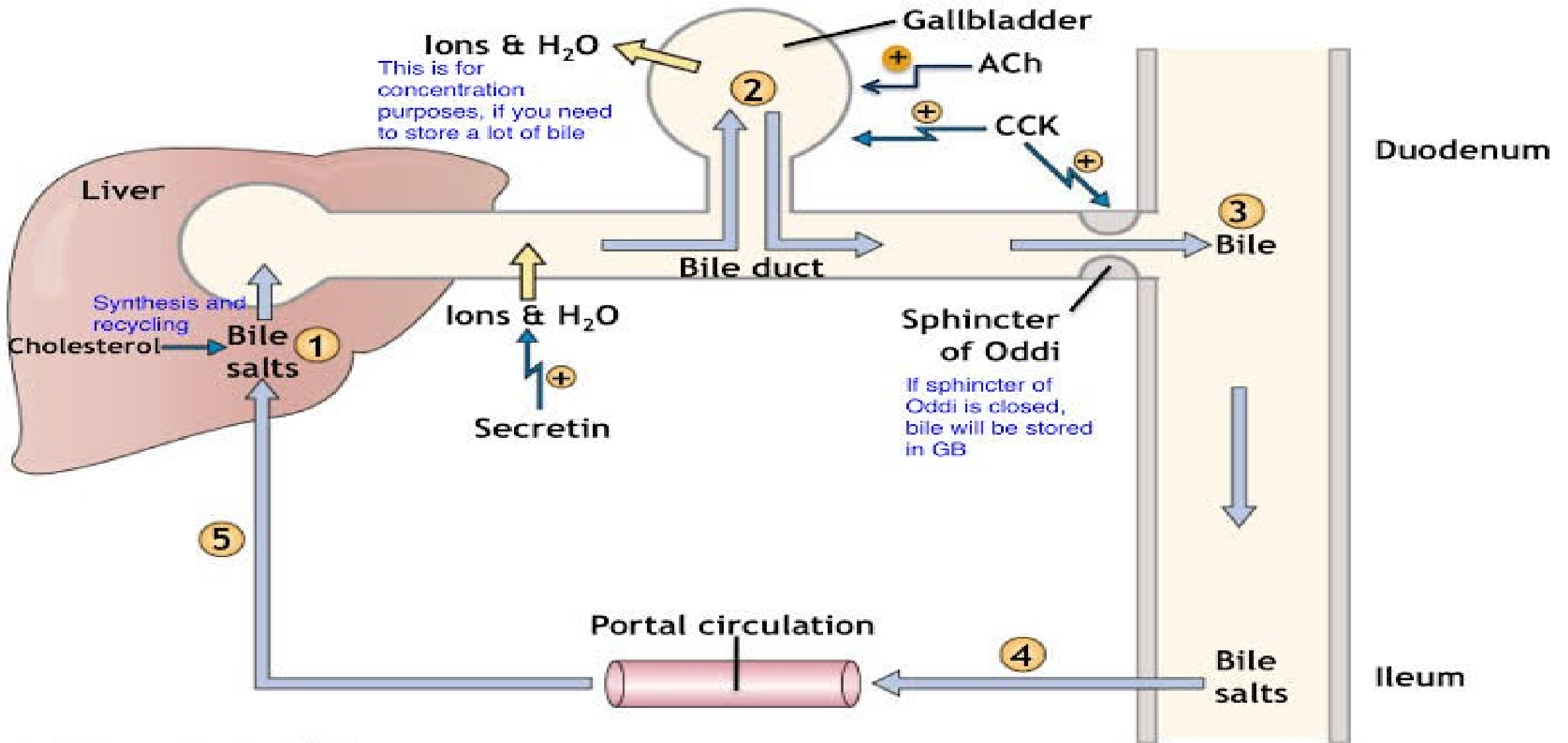


https://www.researchgate.net/profile/John_Chiang2/publication/253339735/figure/fig5/AS:271095169286170@1441645533655/Enterohepatic%20circulation%20of%20bile%20acids.pdf
 N.B.: 95 % of bile salts are reabsorbed by active transport from the terminal

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ileum into the blood & the remaining 5-10% enter the colon





Functions of bile



Most of the functions of bile are due to the **bile salts**

1. DIGESTIVE FUNCTION:-

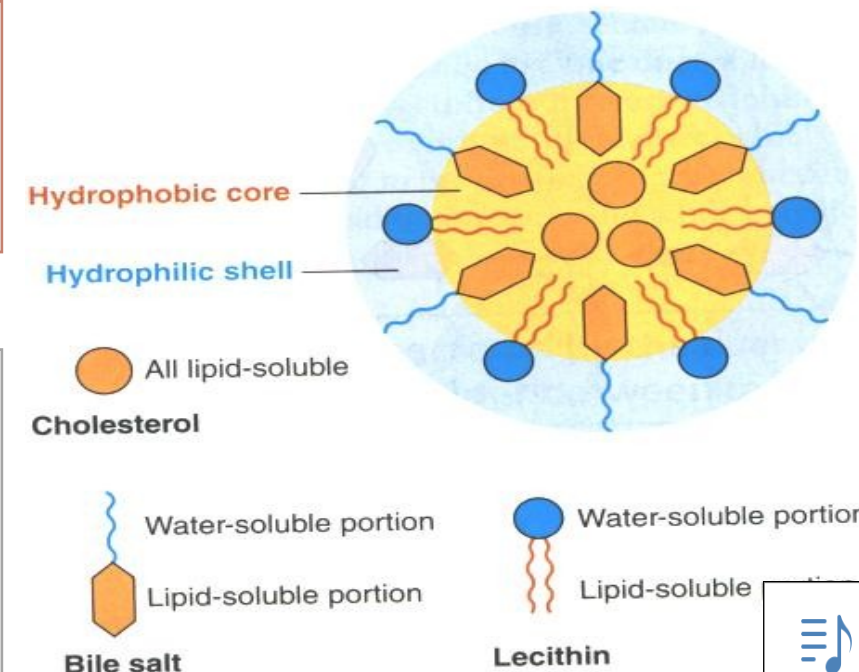
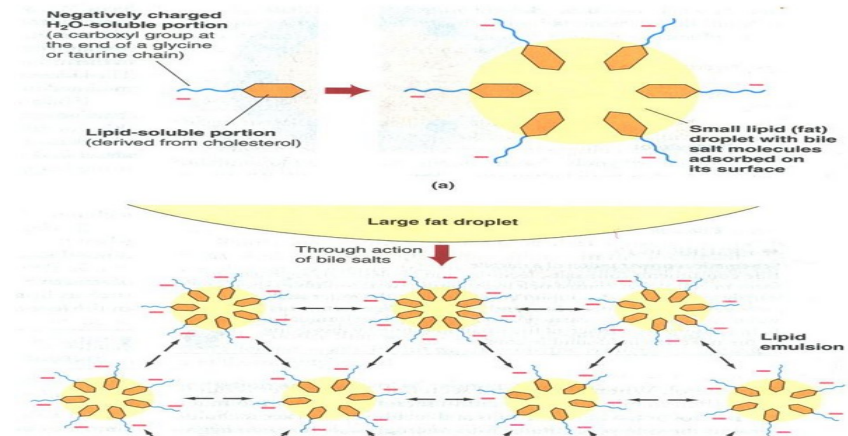
- **Bile salts** play an important role in fat digestion. Emulsify large fat particles into smaller ones that can be attacked by lipase (detergent action)

2. ABSORPTIVE FUNCTIONS:-

- **Bile salts** play an important role in fat absorption. Help in the transport and absorption of fat (micellar formation)

3. EXCRETORY FUNCTIONS:-

- Bile pigments are the major excretory products of the bile
- Other substances excreted in bile are: i. Heavy metals like copper and iron ii. Some bacteria like typhoid bacteria iii. Some toxins iv. Cholesterol v.



Functions of bile



Most of the functions of bile are due to the **bile salts**

4. LAXATIVE ACTION:-

- **Bile salts** act as laxatives by stimulating peristaltic movements of the intestine

5. ANTISEPTIC ACTION:-

- Bile inhibits the growth of certain bacteria in the lumen of intestine by its natural detergent action

6. CHOLERETIC ACTION :-

- **Bile salts** have the choleretic action = stimulate the secretion of bile from liver



Functions of bile



Most of the functions of bile are due to the **bile salts**

7. MAINTENANCE OF pH IN GASTROINTESTINAL TRACT:-

- As bile is highly alkaline “Bicarbonate” , it neutralizes the acid chyme which enters the intestine from stomach. Thus, an optimum pH is maintained for the action of digestive enzymes

8. PREVENTION OF GALLSTONE FORMATION.

- **Bile salts** Prevent precipitation of cholesterol by keeping them in solution (prevent gall stones)

9. LUBRICATION FUNCTION:-

- The mucin in bile acts as a lubricant for the chyme in intestine

10. CHOLAGOGUE ACTION:-

- **Bile salts** act as cholagogues. It causes contraction of gallbladder and release of bile into the intestine indirectly by stimulating the secretion of hormone cholecystokinin



Bile secreted from liver is.....

- Not necessary for normal digestion .
- Important for digestion of protein only
- Stored in gall bladder

Bile secreted from liver is.....

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Effects of surgical removal of terminal ileum



Surgical removal of terminal ileum

Loss of bile salts in feces and deficiency of bile salts

Failure of digestion and absorption of fat

Increase undigested fat in feces

steatorrhea

Failure of absorption of fat soluble vitamins

Decrease vit K absorption

Decrease clotting factors

bleeding

Decrease vit D absorption

Decrease calcium in blood

PTH remove calcium from bone

osteoporosis

Precipitation of cholesterol
In gall bladder

Gall stones



Functions of the gall bladder



Storage of bile

tonical contraction of sphincter of oddi between meals
□ Retrograde flow of bile from cystic duct to be stored in GB

Acidification of bile

HCO_3^- reabsorption, this prevents Ca^{++} precipitation and formation of gall stones

Evacuation of bile

Contraction of the wall and relax of the sphincter of oddi stimulated by **cck** and **vagus**)

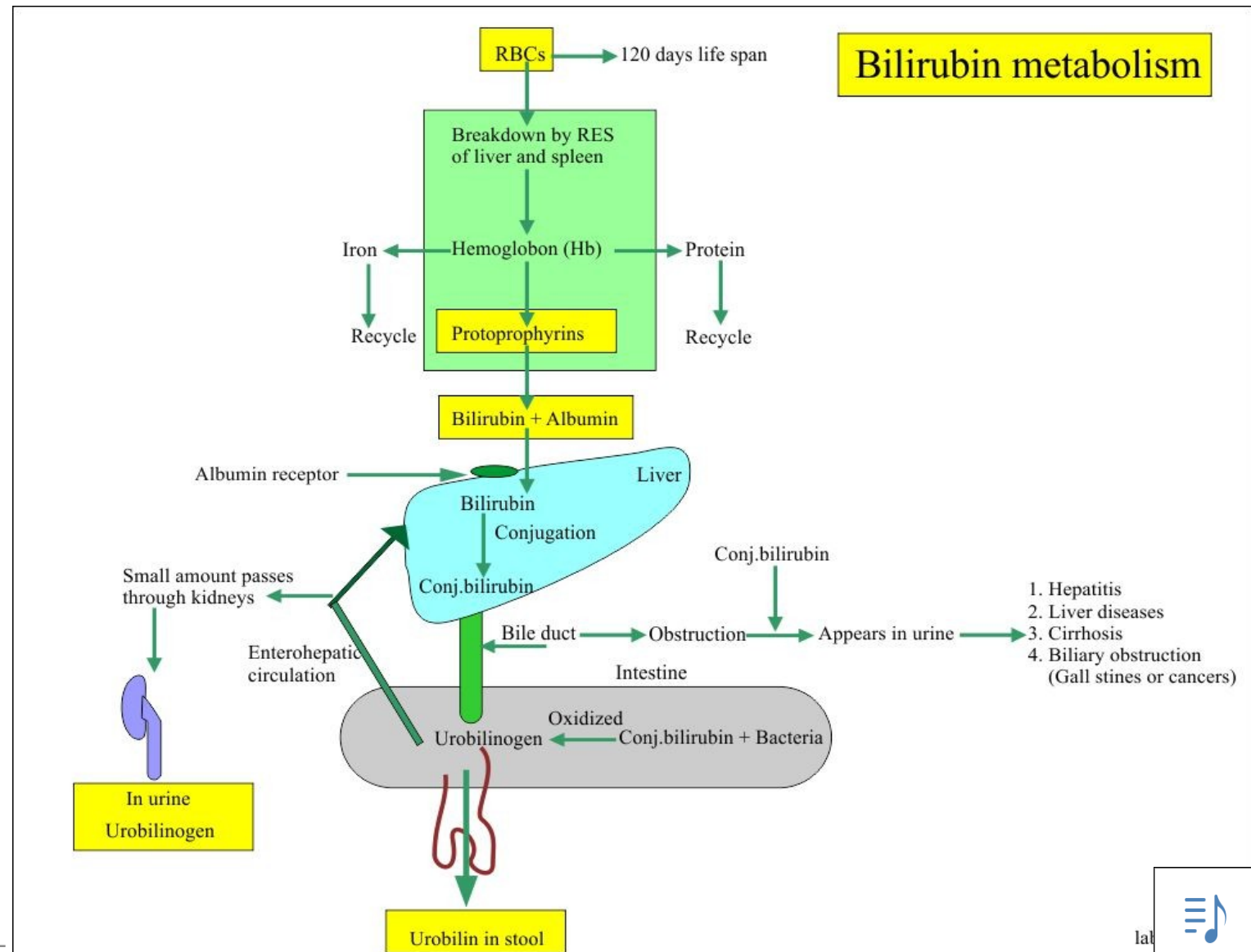
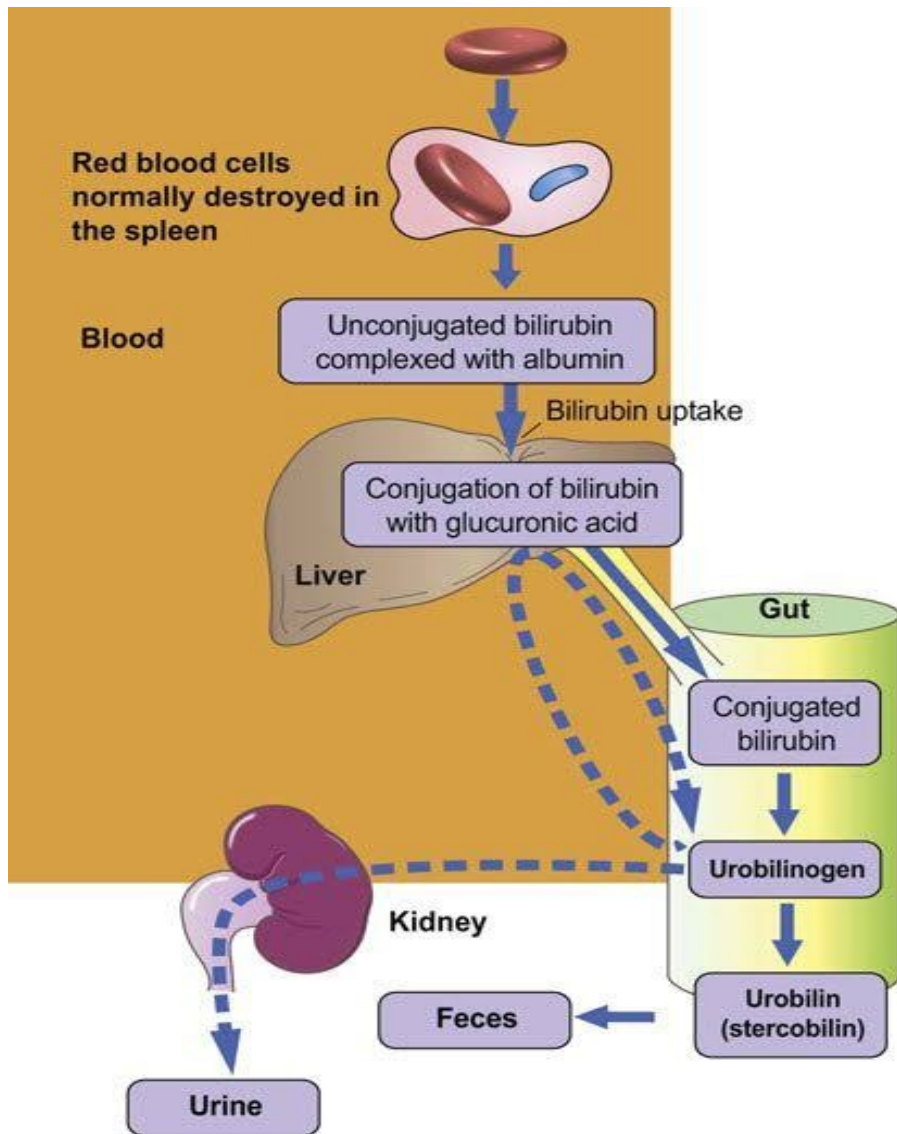
Concentration of bile
active reabsorption of Na^+ followed by passive reabsorption of water and most other electrolytes so the conc. of bile salts in GB increased 5-10 times. This concentration of bile prevent the rise in biliary pressure

Secretion of mucin (white bile)

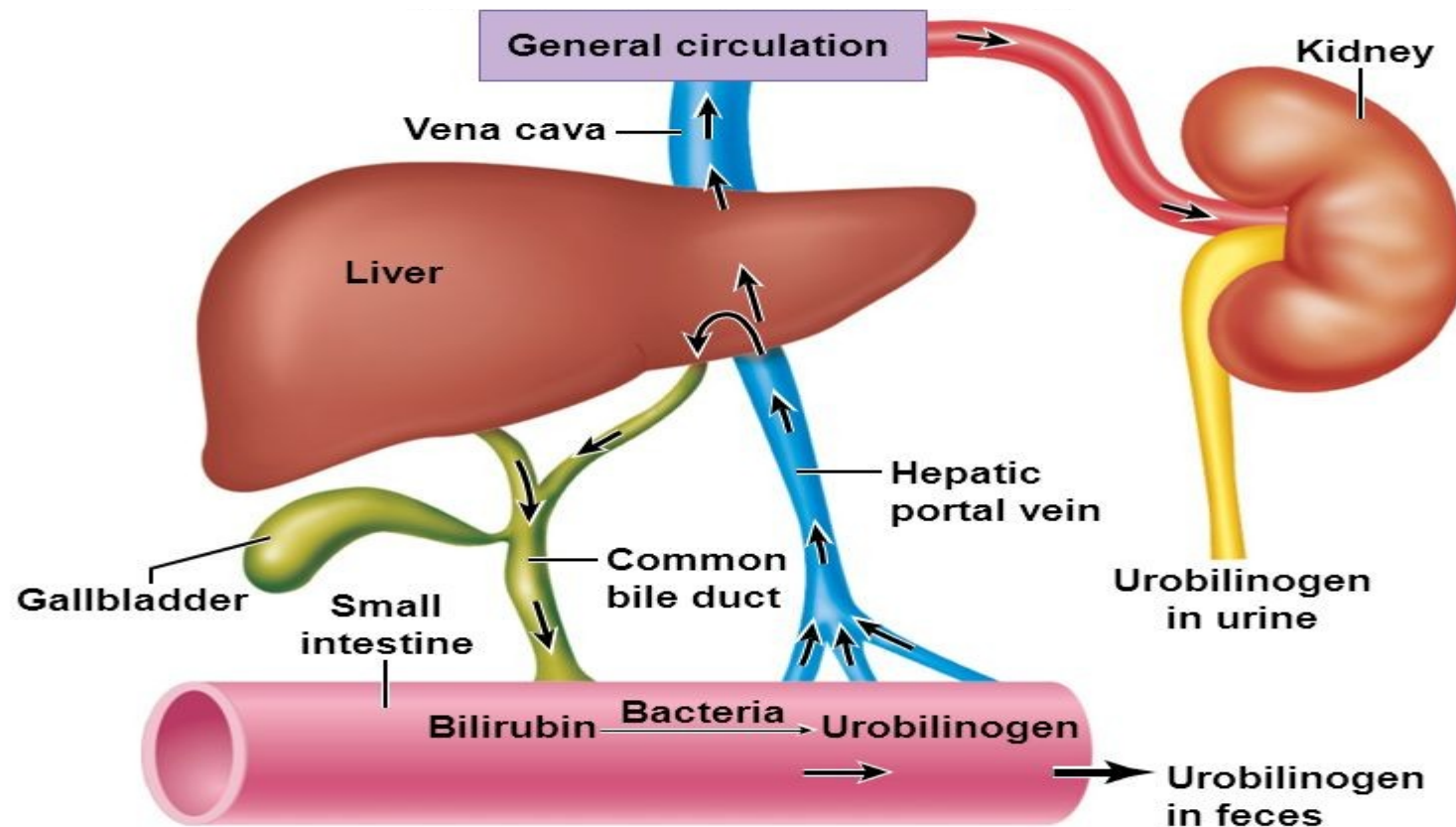
(secreted by GB mucosa protects GB from irritation by acidified concentrated bile, give bile semifluid consistency, in SI act as lubricant and buffer)



Bile pigments & Bilirubin metabolism



Enterohepatic circulation of urobilinogen



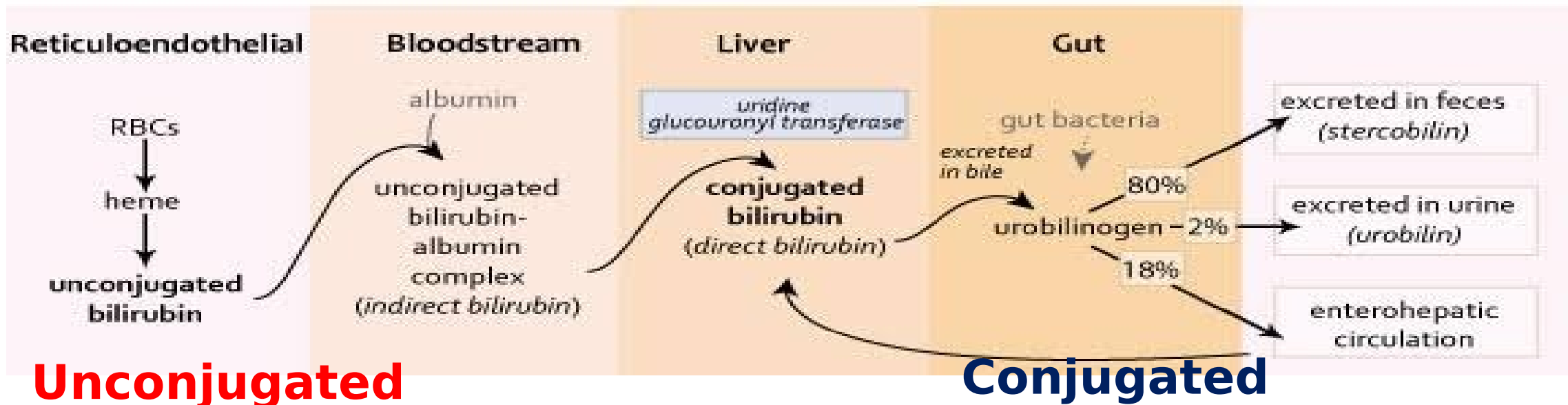
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Bilirubin



Bilirubin



- Hemobilirubin
- Indirect bilirubin
- Free bilirubin
- Insoluble in water
- Tightly complex to albumin
- Cannot be excreted in urine

- ❖ Cholebilirubin
- ❖ Direct bilirubin
- ❖ Water soluble
- ❖ Loosely bound to albumin
- ❖ Excreted in urine (small amount)





Jaundice

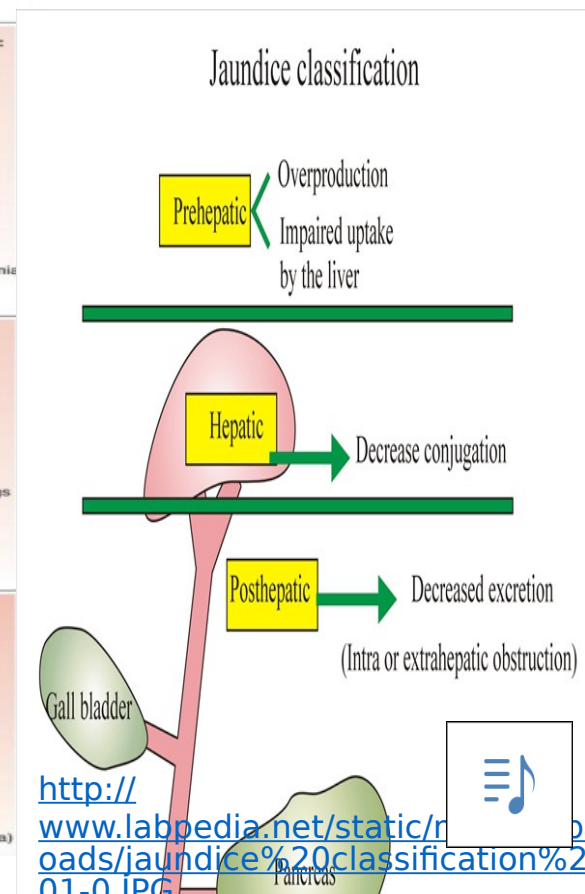
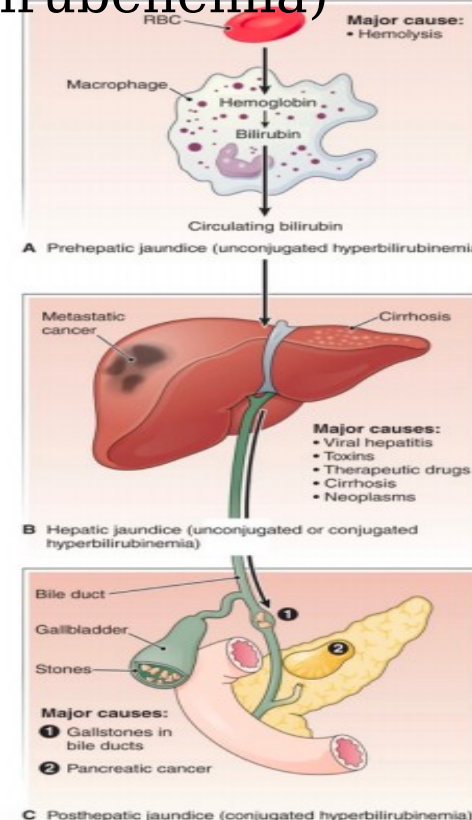


Yellowish colouration of the skin, eye sclera & mucous membranes due to excessive amounts of bilirubin in the blood
 plasma bilirubin is **0.5-1.2mg/dl** (almost free bilirubin) - Normal

- Jaundice appears when bilirubin is above **1.5-2 mg/dl**
- Causes: ↑ free bilirubin (unconjugated hyperbilirubinemia) OR

Category ↑ conjugated bilirubin (conjugated hyperbilirubinemia)

Pre-hepatic/hemolytic	The pathology is occurring prior to the liver, due to either: A. Intrinsic defects in red blood cells B. Extrinsic causes external to red blood cells
Hepatic/hepatocellular	The pathology is located within the liver caused due to disease of parenchymal cells of liver
Post-hepatic/cholestatic	The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage.



Jaundice



Red blood cell destruction



**Exceed the ability of
hepatocytes uptake**



**Blood Free Bilirubin
(Unconjugated)**



Hemolytic





Jaundice

Liver Diseases



Conjugation & Excretion of Bilirubin



Blood Bilirubin (Unconjugated)



Hepatic Jaundice



Jaundice



Common bile duct Obstruction



Bilirubin excretion



Blood Bilirubin (Conjugated)



**Obstructive
Jaundice**



Jaundice



	Haemolytic Jaundice	Hepatic Jaundice	Obstructive Jaundice
causes	Excessive RBCs break down	Liver disease hepatitis , toxic drugs	Obstruction of the common bile duct
Type of excess bilirubin in plasma	Free bilirubin	Free & conjugated bilirubin	Conjugated bilirubin
Depth of color	Mild	Moderate	Sever
Fat digestion	Normal	Moderately impaired	Markedly impaired
Liver functions	Normal	Markedly impaired	Moderately impaired
Urine color	Normal	Darker than normal	Dark brown
Stool color	Dark	Paler than normal	Very pale
Blood	Anemia, reticulocytosis cause of hemolysis	Moderate increase in cholesterol, alkaline phosphatase and bile salts	Marked increase in cholesterol, alkaline phosphatase and bile salts



Liver cell failure



Decreased clotting factors

Bleeding

plasma proteins (albumin)

Edema

liver glycogen

Inability to work

Decreased detoxification of drug

Drug toxicity

Damage to kupffer cell

Systemic infections

Decreased active vitamin D

Osteoporosis

Decreased bile formation

Decreased fat absorption

Decreased conjugation of bilirubin

Jaundice



Lecture Quiz



A 43-year-old overweight woman presents to her doctor's office because of right upper quadrant abdominal pain. She has experienced similar episodes of this type of pain in the past and admits that it is worse after meals. Increased secretion of which of the following is responsible for this patient's postprandial pain?

- a) Cholecystokinin
- b) Decreasing the secretion of gastrin
- c) Pepsin
- d) Somatostatin
- e) Vasoactive intestinal peptide



Lecture Quiz



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SUGGESTED TEXTBOOKS



1. Ganong's "Review of Medical Physiology", 25th edition,
Section V gastrointestinal physiology, Chapter 26
2. Guyton and Hall "Textbook of Medical Physiology", 13th
edition, Chapter 64
3. Sembulingam "Essentials of Medical Physiology", 6th
edition, Chapter 41

